Amendments to the Specification

Please replace the paragraph beginning at page 1, line 13 with the following rewritten paragraph.

International application number PCT/US97/14751 discloses the manufacture of oligonucleotide prodrugs having ester or amide modifications that cover a non-bridging oxygen of the phosphodiester linkage. Kuhn, Oncology, Supplement No. 6, 39-42 (1988) discloses that CPT-11 ~~(Camptosar)~~ irinotecan is an antineoplastic prodrug that is converted by carboxylesterase activity in the liver and other tissues to the active agent SN-38. Cerosimo, The Annals of Pharmacotherapy 32: 1324-1333 (1998) teaches that the parent compound of CPT-11, camptothecin, was unable to be developed as a pharmaceutical due to severe toxicity.

Please replace the paragraph beginning at page 3, line 8 with the following rewritten paragraph.

The methods according to the invention comprise co-administering to the patient a prodrug, preferably an ester or amide prodrug, and a polyanion, preferably a polysulfate. Preferred prodrugs include, without limitation, esters or amides of anti-cancer drugs, such as ~~Camptosar~~ irinotecan and ~~Camtosar~~ irinotecan analogs. Preferred polyanions include, without limitation, heparin, dextran sulfates, suramin sulfates, cyclodextrin sulfates and oligonucleotides, especially oligonucleotide phosphorothioates or phosphorodithioates.

Please replace the paragraph beginning at page 6, line 6 with the following rewritten paragraph.

Preferred prodrugs include amides and esters of active compounds. Such active compounds include, without limitation, anticancer chemotherapeutics, anti-inflammatory agents, antiinfectious agents, antiviral agents and cardiovascular drugs. Numerous prodrugs are well known in the art (see, *e.g.*, Singh *et al.*, *J. Sci. Ind. Res.* **55**: 497-510 (1996)). A non-limiting example of preferred active compounds is SN-38. Specific non-limiting examples of preferred prodrugs include ~~Camptosar~~ irinotecan ((7-ethyl-10-(-4-piperidinol)-1-piperidnocarbonyloxy-camptothecin; CPT-11) and ~~Captosar~~ irinotecan analogs and foscarnate. The moiety that is

cleaved from the prodrug may preferably be selected from esters and alpha-acyloxyalkyl esters (for carboxy functionalities); amides, esters, carbonate sters, phosphate esters, ethers and alpha-acyloxyalkyl ethers (for hydroxy functionalities); thioesters, alpha-acyloxyalkyl thioiesters and disulfides (for sulfhydryl functionalities); ketals, imines, enol esters, oxazoladines, and thiazolidines (for carbonyl functionalities); amides, carbamates, imines enamines N-Mannich bases, and N-acyloxyalkoxycarbonyl derivatives (for amino functionalities); N-acyloxyalkyl derivatives (for quarternary amino functionalities); N-sulphonyl imidates (for ester or sulfonamido functionalities); N-Mannich bases (for NH-acidic functionalities); and N-acyloxyalkyl derivatives (for heterocyclic amino functionalities).

Please replace the paragraph beginning at page 12, line 3 with the following rewritten paragraph.

Female NCr-nude mice, 6-8 weeks of age, were fed *ad libitum* water (reverse osmosis, 0.17% Cl) and an autoclaved standard rodent diet (NIH31) of 18% protein; 5% fat, 5% fiber, 8% ash and 3% minerals. Mice were housed in microisolators on a 12 hour light cycle at 22°C in 40-60% humidity. Mice were implanted subcutaneously in the flank with 1 mm^3 HCT-116 human colon carcinoma fragments in the flank. Tumors were monitored twice weekly initially, then daily as the tumors reached approximately 100 mg in weight. When the tumors reached a weight between 40-221 mg (calculated weight), the animals were pair-matched into the various treatment groups. Estimated tumor weight was determined according to the equation: tumor weight =

$$\frac{w^2 x l}{2}$$

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where w = width and l = length in mm of a HCT-116 tumor. Phosphorothioate oligonucleotides having 2'-O-methylribonucleosides at the 2 terminal 5' positions and 4 terminal 3' positions (Oligo 1), or the 4 terminal 5' and 3' positions (Oligo 2) were prepared according to standard procedures and dissolved in neutral buffered saline. Oligo 1 had the sequence 5'-UGACACCTGTTCTCACUCAC-3' (complementary to mdm-2), and the aequence of Oligo 2 was 5'-UCGCACCCATCTCTCTCCUUC-3' (complementary to the HIV-1 gag gene). ~~Camptosar~~ irinotecan was purchased from Pharmacia & Upjohn.

Please replace the paragraph beginning at page 12, line 23 with the following rewritten paragraph.

Animals were pair-matched on Day 1 into 12 groups with 9 mice per group. Oligo or Oligo 2 was administered i.p. at 10mg/kg doses on a 5/2/5/2/5/2/5 schedule (*i.e.*, five days dosing, two days rest, repeat). ~~Camptosar~~ Irinotecan was administered i.v. at doses of 25 or 50 mg/kg once a week for 3 weeks. For combined treatments, 5 or 10 mg/kg of Oligo 1 was administered i.p. with ~~Camptosar~~ irinotecan at 25 mg/kg, or 10 mg/kg Oligo 1 was administered was administered i.p. with 50 mg/kg ~~Camptosar~~ irinotecan. Oligo 2 was administered at a dose of 10 mg/kg i.p. with 25 or 50 mg/kg ~~Camptosar~~ irinotecan. Control animals were treated with vehicle i.p. on a 5/2/5/2/5/2/5 schedule. The study was terminated on day 56.

Please replace the paragraph beginning at page 13, line 23 with the following rewritten paragraph.

Of the 9 vehicle control mice, 8 had tumors reaching the 1.5 g endpoint with an MDS value of 21.5 days. One tumor regressed completely, presumably due to poor tumor take. ~~Camptosar~~ irinotecan at 25 mg/kg produced an MDS value of 31.1 days, and at 50 mg/kg, 42.6 days. Neither Oligo 1 nor Oligo 2 alone produced any prolongation of MDS. However, administration of 10 mg/kg Oligo 1 with 25 mg/kg ~~Camptosar~~ irinotecan extended MDS over vehicle controls by 24.4 days, and over mice treated with 25 mg/kg ~~Camptosar~~ irinotecan alone by 14.8 days. Each of these extensions is statistically significant ($p < 0.0001$; unpaired t-test). Mice treated with 5 mg/kg Oligo 1 and 25 mg/kg achieved an MDS value of 37.4 days, which

was statistically significant over vehicle controls ($p < 0.0005$; unpaired t-test) and over mice treated with 25 mg/kg ~~Camptosar~~ irinotecan alone ($p < 0.046$; unpaired t-test). Administration of 10 mg/kg Oligo 2 i.p. with 25 mg/kg ~~Camptosar~~ irinotecan produced an MDS value of 39.7 days, which is statistically significant over vehicle controls ($p < 0.0001$; unpaired t-test) and over mice treated with 25 mg/kg ~~Camptosar~~ irinotecan alone ($p < 0.0009$; unpaired t-test). Administration of 10 mg/kg Oligo 2 i.p. with 50 mg/kg ~~Camptosar~~ irinotecan produced an MDS value of 42.6 days, which trends toward statistical significance over mice treated with 50 mg/kg ~~Camptosar~~ irinotecan alone ($p < 0.08$; unpaired t-test). These results demonstrate that both Oligo 1 and Oligo 2 can potentiate the activity of ~~Camptosar~~ irinotecan efficacy in a statistically significant and dose-dependent manner, and that at least part of this effect is independent of oligonucleotide sequence. The results of these studies are summarized in Figures 1-4.

Please replace the paragraph beginning at page 14, line 14 with the following rewritten paragraph.

Comparison of the potentiation of ~~Camptosar~~ irinotecan efficacy by Oligo 1 against potentiation of ~~Camptosar~~ irinotecan efficacy by Oligo 2 shows that there is a statistically significant difference in favor of Oligo 1 ($p < 0.0074$; unpaired t-test). It is believed that this difference may arise from an antisense effect of Oligo 1 on expression of the mdm-1 oncogene to which it is complementary.

Please replace the paragraph beginning at page 15, line 3 with the following rewritten paragraph.

The study was carried out as described in Example 1, except that Panc-1 tumor was used, 4 groups of 10 mice each were used, Oligo 1 and Oligo 2 (in this case, 5'-UCCCACCTATTCTTACUCCC-3', with two 5'-terminal 2'-O-methylribonucleosides and four 3'-terminal 2'-O-methylribonucleosides) were given at doses of 20 mg/kg, ~~Camptosar~~ irinotecan was given at 100 mg/kg, tumor "cut-off" was 1.2 g, and the study was terminated on Day 67.

Please replace the paragraph beginning at page 15, line 9 with the following rewritten paragraph.

Both Oligo 1 and Oligo 2 showed statistically significant potentiation of ~~Camptosar~~ irinotecan efficacy ($p < 0.05$; unpaired t-test). The potentiating effects of Oligo 1 and Oligo 2, compared with each other, were statistically indistinguishable. These results demonstrate that oligonucleotides produce a statistically significant potentiating effect on ~~Camptosar~~ irinotecan that is independent of the sequence of the oligonucleotide. Moreover, in these studies treatment with ~~Camptosar~~ irinotecan alone was not statistically significantly better than treatment with vehicle. Thus, these results demonstrate that oligonucleotides can potentiate the effectiveness of ~~Camptosar~~ irinotecan such that an otherwise sub-therapeutic dosage of ~~Camptosar~~ irinotecan becomes therapeutically effective.

Please replace the paragraph beginning at page 15, line 21 with the following rewritten paragraph.

The study of Example 1 was repeated, but the oligonucleotide was administered initially on day 1 and ~~Captosar~~ irinotecan was not administered initially until day 3. Surprisingly, this schedule of administration was even more effective (see Figure 5). Also, the study of Example 1 was repeated, but the oligonucleotide was administered orally. This route of administration was equally effective (see Figure 6).